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Guidance for Industry

Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

This draft document discusses a recommended approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern.

Comments and suggestions regarding this document should be sent to the Dockets Management Branch (HFA 305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 98D-1146. Submit electronic comments to http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm.

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Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855 and may be viewed on the Internet at http://www.fda.gov/cvm.

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Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern

This document represents the Agency's current thinking on a recommended approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternate approach may be used as long as it satisfies the requirements of applicable statutes and regulations.

I. INTRODUCTION

Food-producing animals are administered antimicrobial drugs for therapeutic, preventive, and production purposes. The use of antimicrobial drugs in food-producing animals is important in helping to promote animal health, welfare, and productivity. However, food-producing animals can serve as reservoirs of both commensal and pathogenic bacteria that may be transferred to humans by consumption of contaminated food products.[1,2,3,4] With the use of antimicrobial drugs in food-producing animals, these bacteria may become resistant to drugs that may also be used to treat human illness, potentially making human illnesses more difficult to treat.[5,6,7,8] In addition, bacteria pathogenic to humans can acquire resistance traits from non-pathogenic bacteria originating in food-producing animals by mechanisms that allow the exchange of their genetic material in the human gastrointestinal tract.[9,10]

Antimicrobial resistance is a complex phenomenon. The selection of antimicrobial resistant bacterial populations occurs as a consequence of the combined impact of antimicrobial drug use in humans, animals, and plants (or other agricultural settings). As a consequence, the human health impact specifically due to the use of antimicrobial drugs in food-producing animals is difficult to assess precisely. Antimicrobial drug resistance has been linked to resistance against non-related antimicrobial drug classes, disinfectants, and other compounds such as heavy metals.[11,12] The use of unrelated drugs can result in the co-selection of multiple drug resistance when resistance determinants (genes) for unrelated drugs are linked. Additionally, since certain mechanisms of resistance affect more than one class of antimicrobial drug (cross-resistance), the use of one particular antimicrobial drug may confer resistance to multiple drugs.[11,13,14]

FDA published as a draft document on November 18, 1998 (63 FR 64094), and as a final document on December 17, 1999 (64 FR 70715), the guidance entitled "Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (Guidance #78). This guidance document signaled a policy change with regard to the safety evaluation of antimicrobial new animal drugs.

Although FDA had considered previously the microbiological effects of certain uses of antimicrobial drugs (21 CFR 558.15), Guidance #78 stated FDA's intention to consider the potential human health impact of the microbiological effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals. The specific microbiological effects considered in Guidance #78 included the impact of antimicrobial drug use in animals on the rate and extent of resistance emergence and on the quantity of bacteria in animals that are pathogenic to humans.

On January 6, 1999, the FDA announced (64 FR 887) the availability of the discussion document entitled "Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (Framework Document). The Framework Document discussed possible strategies for managing the potential risks associated with the use of antimicrobial drugs in food-producing animals. These strategies included: 1) revision of the pre-approval safety assessment for antimicrobial resistance for new animal drug applications to assess all uses; 2) categorization of antimicrobial drugs based upon the importance of the drug for human medicine; 3) post-approval monitoring for the development of antimicrobial drug resistance; 4) the collection of food animal drug use data; and 5) the establishment of regulatory thresholds. FDA has considered all comments from stakeholders related to the Framework Document in the process of developing the draft guidance discussed herein.

Prior to approving an antimicrobial new animal drug application, FDA must determine that the drug is safe and effective. For antimicrobial drugs intended for use in food-producing animals, the Agency must determine specifically that such drug use is safe with regard to human health. FDA considers the drug to be "safe" if it concludes that there is reasonable certainty of no harm to human health from the use of the proposed new animal drug in food-producing animals. This draft guidance document provides guidance for industry on one possible process for evaluating potential microbiological effects of such drugs as part of the new animal drug application process.

Consistent with the Framework Document, FDA also intends to re-evaluate the potential microbiological effects of antimicrobial drug products currently approved for use in food-producing animals and for which antimicrobial resistance concerns were not previously considered. The agency intends to re-evaluate such products using a risk analysis process similar to that described in this document for evaluating drugs prior to approval. Appendix C provides a general description of that process.

II. Scope of Guidance Document

FDA explained previously in Guidance #78 that it intended to consider, as part of the pre-approval safety evaluation process, the potential human health impact of the microbiological effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals. Further clarification is provided below regarding which microbiological effects should be considered and which investigational new animal drugs (INADs) or new animal drug applications (NADAs) are covered by the guidance described herein.

A. Microbiological effects of animal drugs:

1. Antimicrobial resistance: The primary focus of this guidance is to address the concern that the use of antimicrobial new animal drugs in food-producing animals will cause resistance determinants or resistant bacteria to emerge and to impact human health adversely.

2. Other microbiological effects:

   a. Pathogen load effects: Antimicrobial new animal drugs administered to food-producing animals may affect the bacterial populations present in animal intestinal tracts. These effects may include changes in the number of bacteria that are human pathogens (pathogen load). Although this potential microbiological effect of antimicrobial drugs has been acknowledged, there is no scientific consensus regarding the relevance of the effect or regarding methodologies for how such an effect could be measured.

      As a consequence, FDA convened its Veterinary Medicine Advisory Committee (VMAC) in January 2002 to obtain recommendations with regard to potential antimicrobial drug effects on pathogen load. The majority of the committee members concluded that the scientific evidence presented indicates that there is little to no public health significance associated with pathogen load with regard to antimicrobial drug use. The committee recommended that pathogen load studies not be included as part of the pre-approval drug process for either sub-therapeutic or therapeutic drugs. After considering the committee recommendations and other relevant scientific information, the FDA has concluded that, at this time, specific

information regarding potential antimicrobial drug effects on pathogen load should not be included in the pre-approval new animal drug evaluation process. Therefore, pathogen load is not considered within the scope of this draft guidance document.

b. Effects of drug residues on human intestinal microflora: Antimicrobial drug residues present in food from food-producing animals may cause adverse effects on the ecology of the intestinal microflora of consumers.[15,16] As a result of this concern, FDA published a guidance document on January 30, 1996 (61 FR 3043), entitled "Microbiological Testing of Antimicrobial Drug Residues in Food" (Guidance #52). This guidance document stated that the agency would consider antimicrobial activity when establishing tolerances for antimicrobial new animal drugs.

Based on the availability of new information, FDA revised the 1996 guidance and published a new draft guidance for industry (also referred to as Guidance #52) on December 27, 2001 (66 FR 66910) entitled "Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora."

B. New animal drugs covered by this guidance:

The FDA believes that human exposure through the ingestion of resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to resistance determinants (or resistant bacteria) that have emerged as a consequence of antimicrobial drug use in animals. Therefore, FDA's strategies for managing antimicrobial resistance concerns are focused currently on those antimicrobial new animal drugs that are intended for use in food-producing animals. As stated in Guidance #78, this focus includes all uses of antimicrobial new animal drugs in food-producing animals.

C. Antimicrobial NADAs for food-producing animals that may not be subject to this guidance:

There are certain categories or types of antimicrobial new animal drug applications for which additional information may not be needed regarding the microbiological effects outlined above. Such antimicrobial new animal drug applications may include the following:

1. Certain supplemental NADAs: Microbiological safety information typically is not needed for Category I supplemental NADAs (21 CFR 514.106(b)(1)). These supplements ordinarily do not require a reevaluation of any of the safety or effectiveness data in the parent application. However, information may be needed for certain Category II supplemental NADAs (21 CFR 514.106(b)(2)). These supplements may require a reevaluation of certain safety or effectiveness data in the parent application.

2. NADAs for minor species or minor uses: Safety information regarding potential microbiological effects would ordinarily not be needed for NADAs for minor species or minor uses when there is an existing approval for the new animal drug in a major species. However, in certain circumstances information may be requested for drug applications for minor species or minor uses.

3. NADAs for antimicrobial drug combinations: Safety information regarding potential microbiological effects would ordinarily not be needed for antimicrobial drug combinations as defined in Section 512(d) of the Act (21 U. S. C. 360b(d)), as amended by the Animal Drug Availability Act (ADAA) of 1996. Safety with regard to potential microbiological effects would be addressed typically as part of the NADAs for the individual antimicrobial drugs that comprise the combination. However, in certain circumstances information may be requested for drug applications for antimicrobial drug combinations.

4. Generic (abbreviated) NADAs: Microbiological safety information is usually not needed for abbreviated new animal drug applications (ANADAs) for generic antimicrobial drugs, but may be needed for supplemental applications seeking innovative extensions to the conditions of use approved for the pioneer product.

5. Other: Drug sponsors should consult with FDA to determine if information regarding potential microbiological effects is needed for their particular new animal drug application.

III. Risk Analysis Methodology

This guidance document outlines a risk analysis methodology and describes its application as a process for evaluating antimicrobial resistance concerns as part of the overall pre-approval safety evaluation of a new animal drug. The new animal drug sponsor may use this guidance and the methodology described to conduct a qualitative risk assessment as part of the safety evaluation of its proposed drug product. There are many factors that are included in a safety evaluation of a new animal drug. This guidance only addresses one way to evaluate human food safety with respect to the potential microbiological effects of antimicrobial drugs on bacteria of human health concern. Other considerations (i.e., potential toxicity, residues, etc.) are also evaluated as part of the overall human food safety evaluation. The sponsor is also free to demonstrate the safety of its proposed drug product in other ways. If the sponsor elects to use this process, the assessment should be submitted to the INAD file with supporting data as a component of the Human Food Safety technical section or be included in the NADA as part of the sponsor's submission under 21 CFR 514.1(b)(8). The results of this risk assessment can help to determine an overall estimate of risk to allow an informed risk management decision. Evaluation of all available information submitted in support of the NADA may result in actions ranging from approval of the new animal drug to denial of the new animal drug application. The remainder of the document provides guidance on this risk analysis methodology.

A. Background:

The risk analysis methodology outlined in this document is based on the methodology described by the Office of International Epizootics (OIE) Ad Hoc Group on Antimicrobial Resistance.[17] The risk analysis methodology described in the OIE document is tailored to address antimicrobial resistance in animals and includes hazard identification, risk assessment, risk management, and risk communication. Although it differs somewhat organizationally, the OIE approach includes similar steps to describe the risk assessment process as the risk analysis paradigm described by the National Academy of Science/National Research Council (NAS/NRC).[18]

The risk assessment process is comprised of a release assessment, exposure assessment, consequence assessment, and risk estimation (See Figure 1). The risk estimation integrates the components of the risk assessment into an overall conclusion that provides a qualitative indication of the potential risk of the proposed antimicrobial new animal drug to human health. The overall risk estimation ranking is then used by FDA, along

with other relevant data and information submitted in support of the NADA, to determine whether the drug might be approvable under specific risk management conditions.

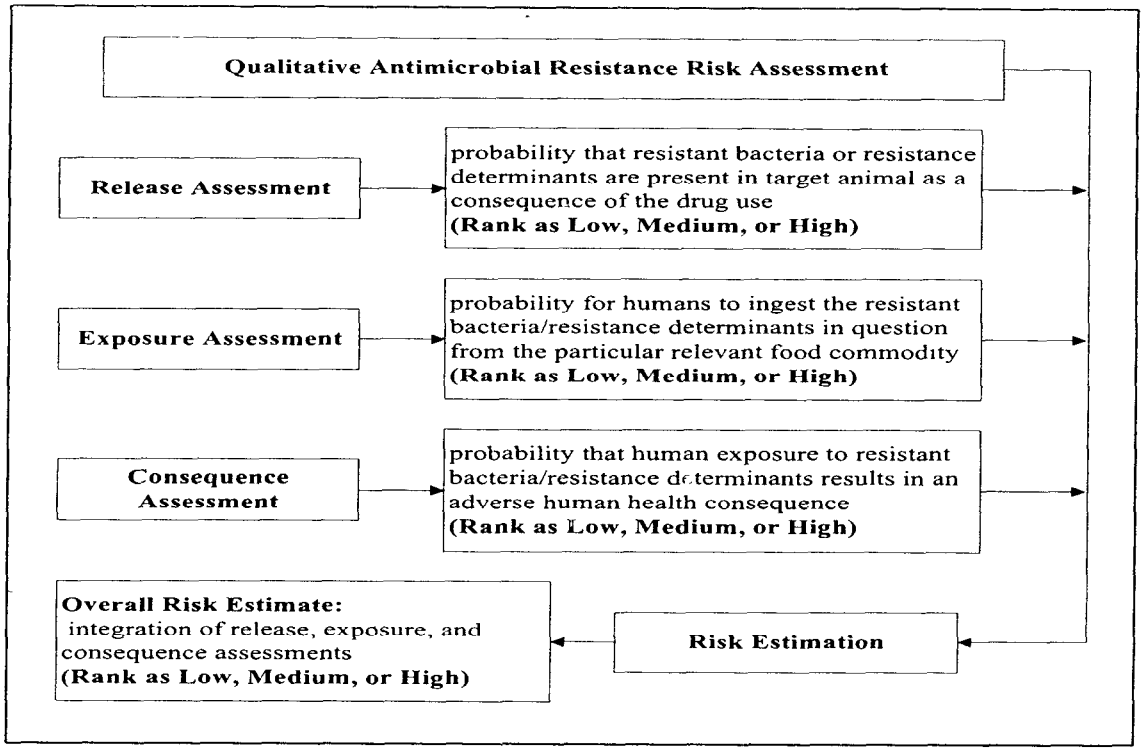

Figure 1. Components of a qualitative antimicrobial resistance risk assessment

B. Definitions:

1. Hazard: The hazard is defined as human illness that is caused by a specified antimicrobial-resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

2. Hazardous agent: The hazardous agent is the antimicrobial-resistant bacteria or resistance determinant(s) of human health significance that arises in a food-producing animal as a consequence of animal uses of antimicrobial new animal drugs. A resistance determinant is a gene that, through either activation, mutation, or external acquisition, provides a bacterium with the necessary biochemical mechanism to survive in the presence of an antimicrobial drug that would otherwise result in the death or inhibition of a susceptible bacterium.

The antimicrobial resistance determinant(s) may be carried on chromosomal or on extra-chromosomal DNA of pathogenic or commensal bacteria. For example, the resistance determinants of interest in this guidance include those expressed in human pathogens (e.g., *Salmonella*, *Campylobacter*) or determinants that are expressed in commensal bacteria (e.g., *E. coli*, *Enterococcus* spp.).

3. Risk: FDA's overriding concern is that the effectiveness of antimicrobial drugs is decreased or lost in humans as a consequence of human exposure to resistant bacteria (or resistance determinants) resulting from the use of antimicrobial drugs in food-producing animals.

   Loss of antimicrobial drug effectiveness, as it is referred to here, is a general concept that might encompass a range of deleterious effects (e.g., increased duration of illness, treatment failure, loss of therapeutic options, etc.) that antimicrobial resistance determinants might have on human health. Due to the difficulties associated with measuring loss of effectiveness, the risk assessment process described here uses a more readily understood and estimated health effect endpoint.

   To that end, we define the risk as the probability that human illness is caused by a specified antimicrobial resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

C. Data sources/data quality:

The data supporting the risk analysis may come from published literature. FDA recommends that drug sponsors refer to Guidance for Industry #106, "The Use of Published Literature in Support of New Animal Drug Approval" for guidance regarding use of published literature. If data are not readily available from published literature or previously conducted studies, sponsors may consider generating necessary data through the conduct of prospective studies. Drug sponsors should refer to 21 CFR 58 for requirements related to Good Laboratory Practices for conducting non-clinical laboratory studies.

IV. HAZARD IDENTIFICATION

Prior to initiating the risk assessment, the sponsor that elects to use this process should identify the hazard and the conditions that influence the occurrence of that hazard.

As previously defined, the hazard is human illness that is caused by a specified antimicrobial-resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

FDA recommends that the hazard identification step of the risk assessment include the following information regarding the chemical, biochemical, and physical properties of the drug that bear on characterizing the downstream effects of the drug:

A. Drug-specific information:

FDA recommends that the sponsor provide information regarding the proposed antimicrobial drug substance that includes:

1. Chemical name and structure

2. Class of antimicrobial drug (e.g., macrolide)

3. Mechanism (e.g., protein synthesis inhibitor) and type of action (i.e., bactericidal vs. bacteriostatic)

4. Spectrum of activity (i.e., Gram-positive, Gram-negative, broad, etc.)

5. Specific susceptibility data (i.e., minimum inhibitory concentrations (MIC) and minimum bactericidal concentration (MBC) data pertinent to pathogens/commensals in question)

   Additional guidance on susceptibility testing may be obtained from recognized sources, if available, such as the NCCLS M37-A2 document "Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline – Second Edition". The M37-A2 document describes the data needed for selection of appropriate interpretive standards and provides quality control guidance for new veterinary antimicrobial agents.

6. Relative importance of the drug to human medicine. Knowledge regarding the relative importance of the drug to human medicine may be important for

interpreting the significance of certain information included in the risk assessment. Refer to human medical importance ranking in Appendix A.

(Note: The human importance ranking will also be incorporated in the consequence assessment component of the risk assessment described below.)

B. Bacteria/resistance determinants information:

Considering the target animal species and the antimicrobial properties of the drug in question, FDA recommends that the sponsor identify:

1. Bacterial species and strains for which resistance acquisition has potential human health consequence.

2. Resistance determinants with human health significance that may be selected for and maintained as a consequence of the animal drug use. It is recommended that information be included that describes any phenotypic and genetic homologies with resistance determinants in other bacteria of human concern.

C. Antimicrobial susceptibility testing methodology:

FDA recommends that the sponsor include the antimicrobial susceptibility testing methodology for the bacterial isolates of concern. The methods may include citations, if available, of relevant laboratory standards such as the National Committee on Clinical Laboratory Standards (NCCLS). Additional guidance on susceptibility testing may be obtained from recognized sources such as the NCCLS M37-A2 document "*Development of In Vitro Susceptibility Testing Criteria and Quality Control Parameters for Veterinary Antimicrobial Agents; Approved Guideline—Second Edition*". The M37-A2 document describes the data needed for selection of appropriate interpretative standards and provides quality control guidance for new veterinary antimicrobial agents. Also, refer to NCCLS M31-A2 document "*Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard —Second Edition.*" The M31-A2 document provides the currently recommended techniques for antimicrobial agent disk and dilution susceptibility testing, criteria for quality control testing, and interpretive criteria for veterinary use.

D. Data gaps and emerging science:

FDA recommends that the sponsor attempt to identify data gaps and areas where additional information may affect current determinations.

V. Qualitative Antimicrobial Resistance Risk Assessment

Based on the hazard, as specifically defined in the Hazard Identification step, the sponsor of the new animal drug electing to use this process should complete a qualitative antimicrobial resistance risk assessment and submit this assessment to FDA for review. The assessment process outlined below adapts the OIE methodology to provide a mechanism for conducting a qualitative pre-approval drug risk assessment. The assessment process described below is intended to organize and integrate an array of relevant information and provide a general method describing how this information may be interpreted. The risk assessment process is comprised of a release assessment, exposure assessment, consequence assessment, and risk estimation (refer to Figure 1).

This assessment process is presented in a simplified format. Sponsors are expected to adapt and expand their risk assessment protocol to accommodate unique interrelationships that may exist between a new antimicrobial drug, affected microbe(s), proposed condition(s) of use and other parameters potentially impacting human health. The assessment process outlined below is intended to result in an overall estimation of the level of concern associated with the development of antimicrobial resistance as a consequence of the proposed use of the drug in animals. This process may help guide the selection of appropriate risk management steps.

FDA intends to determine the appropriate use conditions or other risk management steps based on its review of the risk assessment and consideration of the new animal drug application as a whole.

A. Release Assessment:

The release assessment describes the probability that factors related to the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the animal.

1. Defining the boundaries of the release assessment:

The release assessment should characterize the source of the defined hazardous agent. For the purposes of this guidance, FDA is focusing on the food-producing animal as a source of human exposure to the hazardous agent.

The boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or animal-derived food is collected.

Human exposure to that hazardous agent should be addressed in the exposure assessment.

2. Factors to consider in release assessment:

   For the purposes of this risk assessment, a number of relevant factors are suggested for consideration in completing the release assessment. These factors include factors considered as part of the hazard identification. The sponsor may wish to consult with FDA to determine the specific factors that are most relevant to the new animal drug in question. The sponsor or FDA may consider different factors to take into account any specific considerations pertinent to the drug and its proposed conditions of use. The relative significance of any particular factor among all factors pertinent to the release assessment may vary depending on the specific new animal drug under consideration. Therefore, certain factors may carry greater weight than other factors when determining the overall release assessment ranking. FDA recommends that the pertinent factors considered in the release assessment include, but not be limited to, the following:

   a. Product description: FDA recommends that the sponsor provide information regarding the proposed drug product that includes:

      - Product formulation (active and inactive ingredients)
      - Information regarding proposed conditions of use including:
        - Route of administration (i.e., injection, water, feed)
        - Dosing regimen
        - Proposed product indication
        - Intended target animal species

   b. Drug substance description: FDA recommends that the sponsor provide information regarding the proposed antimicrobial drug substance that includes:

      - Class of antimicrobial drug (e.g., macrolide)
      - Chemical name, CAS number, and structure

   c. Mechanism and type of action: FDA recommends that the sponsor provide information regarding the mechanism of antimicrobial activity that includes:

      - Specifics known regarding antimicrobial mechanisms (e.g., protein synthesis inhibitor)
      - Type of action (i.e., bactericidal action vs. bacteriostatic)

d. Spectrum of activity: FDA recommends that the sponsor provide information regarding spectrum of activity that includes:

- General data (i.e., is activity Gram-positive, Gram-negative, broad, etc.)
- Specific susceptibility data (i.e., minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data pertinent to pathogens/commensals in question). As stated before, refer to appropriate NCCLS documents.

e. The pharmacokinetics/pharmacodynamics of the drug: FDA recommends that the sponsor provide relevant information regarding such factors as:

- absorption, distribution, metabolism, and elimination of the drug in the target animal
- antimicrobial drug activity in colonic contents at different treatment and post-treatment time points
- first-exposure effects, post-antibiotic effects, etc.

f. Resistance mechanisms and genetics: FDA recommends that the sponsor provide information regarding the mechanism(s) and genetic basis of resistance development that includes:

- Known mechanism(s) for resistance (e.g., antimicrobial inactivation, alteration of the drug target, reduced uptake, efflux of the antimicrobial drug, etc.)
- Location of resistance determinants (e.g., plasmid-mediated vs. chromosomal; present on transposon, integron, or phage)

g. Occurrence and rate of transfer of resistance determinants: FDA recommends that the sponsor provide information to help characterize whether resistance determinants are transferable and, if so, at what rate. Relevant questions may include:

- Can resistance determinants be transferred among bacteria by transformation, transduction, conjugation, or transposition?
- If resistance occurs by point mutation, at what rate do the point mutations occur?

h. Resistance selection pressures: FDA recommends that the sponsor provide information to help characterize the relative magnitude of selection pressure for resistance that may exist for the particular drug use in question. Pertinent information may include:

- Information known regarding other antimicrobials that may co-select for resistance
- Information known regarding cross resistance to other antimicrobial drugs approved in veterinary and human medicine
- Consideration of the extent of use of the proposed product (e.g., duration of administration; individual vs. small groups vs. flocks/herds)

i. Baseline prevalence of resistance: FDA recommends that the sponsor provide available epidemiological data outlining the existing prevalence of resistance to the drug in target pathogens and commensal gut flora. This may be obtained from National Antimicrobial Resistance Monitoring System (NARMS) data, current literature, or other sources. If baseline data is not available for their proposed antimicrobial drug, sponsors may wish to consult with FDA regarding the generation of such data.

j. Other information relevant to the release assessment:

Relevant additional information relating to the rate of resistance development and decline after treatment may include:

- Information or studies to characterize the rate of resistance development in bacteria of human health concern.
- Information or studies to characterize the decline of resistance in bacteria of human health concern following cessation of therapy. Of particular interest is information relative to the interval up to the earliest time point (post-drug administration) at which animals would be presented for slaughter.

3. Summarizing the Release Assessment:

FDA recommends that the sponsor characterize qualitatively all factors relevant to the release assessment based on supporting information. It is recommended that this characterization estimate whether each factor would have a high likelihood of favoring resistance emergence, have a low likelihood of favoring resistance emergence, or have an intermediate impact on resistance emergence. For example, the spectrum of activity of the drug might be ranked high for favoring resistance

emergence if the new animal drug in question displays a broad spectrum of activity towards multiple organisms. Conversely, pharmacodynamics might be ranked low with regard to impact on resistance if the same drug did not enter the target animal intestinal tract at concentrations shown to have an effect on resistance development. FDA recommends that the sponsor provide a detailed discussion of the conclusions as well as present the conclusions in summary format (See Table 1 as an example).

Note: If sufficient information regarding a factor is not available or has not been generated for the assessment, the most conservative significance of the particular factor may be assumed. That is, the factor would be assumed to have a high likelihood of contributing to resistance emergence.

4. Release Assessment conclusion:

The outcome of the release assessment is intended to estimate the probability that resistant bacteria or resistance determinants will occur in animals as a consequence of the proposed drug use in animals. FDA recommends that the sponsor use the conclusions obtained from assessing all relevant factors to derive an overall qualitative ranking for the release assessment. This overall conclusion may be expressed in terms of there being a low, medium, or high probability of release of the hazardous agent.

Table 1. Table for collating and summarizing interpretation of relevant factors considered in completing release assessment

Relevant parameters	Extent to which relevant factors favor resistance emergence
	Comments/conclusions regarding factors
Mechanism of activity	
Spectrum of activity	
Pharmacokinetics	
Pharmacodynamics	
Resistance mechanism(s)	
Resistance transfer	
Selection pressure	
Other factors[1]	

[1]Other parameters may be identified in certain cases that are believed to be of particular importance to the evaluation. The sponsor may wish to consult with FDA

regarding additional parameters prior to completing the assessment (e.g., in product development meetings).

B. Exposure Assessment:

The exposure assessment describes the likelihood of human exposure to the hazardous agent through particular exposure pathways. The exposure assessment should provide a qualitative estimate of the probability of this exposure occurring. The hazardous agent is defined as the antimicrobial resistance determinant(s) of human health significance that arises in a food-producing animal as a consequence of animal uses of antimicrobial new animal drugs. The division of traditional exposure assessment into "release" and "exposure" components effectively produces a natural placement of animal and animal treatment factors into the "release assessment component" and food-chain and human factors within the "exposure assessment component."

1. Current focus of exposure assessment:

At this time, assessing human exposure to the hazardous agent should focus on food-related pathways. FDA believes that human exposure through the ingestion of resistant bacteria from animal-derived foods represents the most significant demonstrable pathway for human exposure to resistant bacteria or resistance determinants as a consequence of drug use in food-producing animals.

FDA recognizes that human exposure to antimicrobial resistant bacteria (or resistance determinants) is complex and often involves the contributions from other sources of exposure (e.g., human/animal direct contact, introduction of resistant bacteria and resistance determinants into the environment). However, FDA believes that evaluating drug safety relative to the most significant exposure pathway (i.e., food-borne pathway) is the best way to assess qualitatively the risk of antimicrobial drug use in food-producing animals. Uncertainties regarding the contribution of other potential pathways of exposure may be considered during the development of appropriate risk management strategies.

2. Factors to consider in exposure assessment:

The exposure assessment may be accomplished by integrating information that characterizes:

a. The probability for humans to be exposed to given bacteria via a particular food commodity.

This factor is independent of drug use in animals and may be estimated by considerations of 1) the probability of contamination of food product by the bacteria of interest and, 2) the per capita consumption of the food commodity. While it is acknowledged that other factors such as food preparation practices can affect exposure, the above two considerations can provide a qualitative indication of the magnitude of the probability of human exposure. Survey data of both food commodity contamination and per capita consumption may be submitted to support a qualitative ranking of the probability of human exposure to the given bacteria via a particular food commodity. Refer to Appendix B for examples of how such information may be integrated.

b. Probability that bacteria of interest (to which humans are exposed) are resistant to particular antimicrobial drug or possess associated resistance determinants.

FDA recommends that the sponsor rank qualitatively (i.e., low, medium, high) this probability by one of the following methods:

(1) Base the ranking on specific and current susceptibility data on bacterial isolates obtained from animal-derived food commodities

Since this represents a more direct measure, use of this type of information is recommended when available. This information may be available, for example, in a case where the same or related drug has already been approved in animals and has been in use under similar conditions.

OR

(2) Base the ranking on the conclusions of the release assessment

When susceptibility data as described in (1) above are not available, the conclusions derived from the release assessment may be applied here as an indicator of the probability of resistance associated with the animal-derived food.

The release assessment characterized the probability that the bacteria of concern in/on the animal when presented for slaughter would be resistant or carry resistance determinants (as a consequence of drug use). It is recognized that there are many factors that may affect the bacteria of interest between the time animals are presented for slaughter (or the animal-derived food is collected) and the time the final food product is consumed. For the purposes of this qualitative risk assessment, FDA assumes that the probability that bacteria in the animal at slaughter will be resistant may be used as an estimate

of the probability that the same bacterial species would be resistant in the food commodity derived from that animal.

3. Summarizing the Exposure Assessment:

FDA recommends that the sponsor integrate the two key factors cited above (i.e., probability of exposure to the bacteria and probability that bacteria are resistant) to characterize the probability of human exposure to the identified hazardous agent(s).

That is, FDA recommends that the sponsor derive the exposure assessment ranking by integrating the ranking for the probability of human exposure (through food) to the bacteria in question with the probability that the bacteria will be resistant to the drug in question. This integration may be accomplished through the use of Table B4 in Appendix B and Table 2 below.

Table 2. Process for characterizing the probability of human exposure to the identified hazardous agent (i.e., specified resistant bacteria or resistance determinants).

	Probability of human exposure to the hazardous agent		
	Probability of human exposure to given bacteria[2]		
Probability that bacteria of interest are resistant[1]	**High**	**Medium**	**Low**
High	H	H	M
Medium	H	M	L
Low	M	L	L

[1]May be based on susceptibility data on bacterial isolates from food commodity or on the outcome of the Release Assessment

[2]Ranking from Table B4 in Appendix B

4. Exposure Assessment conclusion:

The exposure assessment ranking may be expressed as low, medium, or high probability of human exposure to the hazardous agent.

C. Consequence Assessment

The consequence assessment describes the relationship between specified exposures to a biological agent (the hazardous agent) and the consequences of those exposures. For the purposes of this risk assessment, FDA believes that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.

Certain antimicrobial drugs are considered to be of greater importance to human medical therapy than other antimicrobial drugs. Therefore, it is assumed that the human health consequences of human illness due to antimicrobial resistant bacteria are more significant if the resistance is to a drug that is important for treating disease in humans.

The sponsor should refer to Appendix A of this document for information related to assessing the importance of the drug in question for human medicine. FDA recommends that the consequence assessment conclusion be based on the human medical importance ranking and be expressed as a high, medium, or low ranking.

D. Risk estimation:

The risk estimation integrates the results from the release assessment, exposure assessment, and consequence assessment to produce an overall estimate of the risk. All three elements of the risk assessment process are important contributing factors and should be integrated and considered as a whole when assessing the risk.

FDA recommends that the risk estimation process rank drugs as low, medium, or high risk. The risk rankings represent the relative potential for human health to be adversely impacted by the emergence of antimicrobial resistance associated with the use of the drug in animals.

Table 3 provides a method for integrating the possible outcomes of the release, exposure, and consequence assessments into a single risk estimation ranking. The distribution of risk estimation rankings listed in Table 3 is intended to provide an initial indication as to how the rankings may be integrated. Further refinement of the risk estimation ranking may be necessary for specific cases based on available information. The following provides the Agency's rationale for the risk estimation rankings provided in Table 3.

1. A risk estimation ranking of *low:*

Drugs ranked low for risk estimation include those ranked low for all three components of the risk assessment as well as those ranked low for two components and medium for the third component. FDA believes that a single

medium ranking when the other two risk assessment components are ranked low should not increase substantially the overall level of risk. Therefore, combinations involving two low ranks and one medium are consistent with an overall risk estimation ranking of low.

2. A risk estimation ranking of *high:*

   Drugs ranked high for risk estimation include those ranked high for all three components of the risk assessment as well as those ranked high for two components and medium for the third component. FDA believes that a single medium ranking when the other two risk assessment components are ranked high should not decrease substantially the overall level of risk. Therefore, combinations involving two high ranks and one medium are consistent with an overall risk estimation ranking of high.

3. A risk estimation ranking of *medium:*

   As listed in Table 3, the largest number of possible risk estimation outcomes is assigned the medium ranking. Drugs ranked medium for risk estimation include those drugs ranked medium for all three risk assessment components as well as those ranked high for one, medium for another, and low for the third component. FDA considers these combinations to represent a medium overall risk due to the intermediate nature of the three rankings considered collectively.

   The drugs assigned a medium ranking in Table 3 also include drugs with risk assessment outcomes that include a number of combinations of high, medium and low rankings. These combinations do not fit obviously into either the low or high risk overall rankings. Therefore, these combinations are also included among those that are considered of medium risk overall.

4. Refining risk estimation rankings:

   Although applicable to all risk estimation rankings, medium risk estimation rankings in particular, may be subject to further refinement based on a consideration of all factors relevant to the specific case in question. For example, certain drugs ranked medium based on Table 3 may ultimately be assigned a high or low ranking if factors are identified that warrant that the risk ranking be modulated up or down. A consideration of certain factors specific to the case in question may warrant the assignment of greater (or lesser) weight to one of the components of the risk assessment. Such a modification in the weight or contribution of the release,

exposure, or consequence assessments may result in a change in the overall risk estimation ranking.

Table 3. Provisional risk estimation rankings based on the integration of the release, exposure, and consequence assessment rankings

Release	Exposure	Consequence	Risk Estimation
low	low	low	low
low	low	medium	low
low	medium	low	low
medium	low	low	low
low	low	high	medium
low	medium	medium	medium
low	medium	high	medium
low	high	low	medium
low	high	medium	medium
low	high	high	medium
medium	medium	low	medium
medium	medium	medium	medium
medium	medium	high	medium
medium	low	high	medium
medium	low	medium	medium
medium	high	low	medium
medium	high	medium	medium
high	low	low	medium
high	low	medium	medium
high	low	high	medium
high	medium	low	medium
high	medium	medium	medium
high	high	low	medium
medium	high	high	high
high	medium	High	high
high	high	medium	high
high	high	high	high

VI. ANTIMICROBIAL RESISTANCE RISK MANAGEMENT CONSIDERATIONS

The qualitative antimicrobial resistance risk assessment process provides for the ranking of proposed antimicrobial new animal drugs with regard to the level of risk that their use will cause an adverse impact on human health. All elements of the risk assessment process (i.e., release, exposure, and consequence assessments) should be integrated and considered as a whole when assessing the risk. This integration process, described previously as the risk estimation, qualitatively assigns a high, medium, or low risk ranking to the proposed new animal drug. This risk ranking can be used to help identify the steps necessary to manage the risks associated with the approval of a given antimicrobial drug.

This section of the guidance describes various risk management steps and outlines how these steps might be applied to manage the specified level of risk. Table 5 below creates three categories (i.e., Category 1, 2, and 3) for antimicrobial new animal drugs intended for use in food-producing animals. These categories associate the drug risk ranking (i.e., high, medium, or low risk) with a set of possible risk management strategies.

Antimicrobial new animal drugs that are ranked as high risk might only be considered approvable under the limited set of conditions outlined for Category 1 drugs. The basis for concluding that a drug should be ranked as high risk include such factors as 1) a moderate to high probability that antimicrobial resistance would emerge in the animal in association with the proposed drug use (release assessment), 2) a moderate to high probability that humans would be exposed to antimicrobial-resistant bacteria or associated resistance determinants through food (exposure assessment), and 3) the finding that the potential consequences of exposure to human health would be moderate to high. In addition, to reach a finding of high risk overall, two of the three major components of the risk assessment would have been ranked high and the third component ranked medium. As previously discussed, FDA believes that a single medium ranking when the other two risk assessment components are ranked high should not substantially decrease the overall level of risk. Therefore, combinations involving two high ranks and one medium are consistent with an overall risk estimation ranking of high.

FDA believes that the NADA for certain antimicrobial drugs ranked as high risk might still be considered approvable if FDA can conclude that after evaluating all supporting information there is a reasonable certainty of no harm when the drug is approved under specific use conditions (e.g., such as those outlined for Category 1 drugs). Such a determination would be made on a case-by-case basis and on a review of the entire application. Although drugs in this category may include those that are moderately or highly important to human medicine, FDA believes that there may be some circumstances where the proposed conditions of use outlined for Category 1 drugs might be determined to be

sufficiently restrictive to minimize resistance emergence in the animal and thereby prevent the effect of resistance on human health.

FDA believes that the NADA for certain antimicrobial drugs ranked as low risk might be considered approvable if FDA can conclude that after evaluating all supporting information there is a reasonable certainty of no harm when the drug is approved under specific use conditions (e.g., such as those outlined for Category 3 drugs). For a drug to be ranked as low risk overall, two of three major components of the risk assessment would have been ranked as low and the third component ranked moderate. FDA believes that a single medium ranking when the other two risk assessment components are ranked low should not substantially increase the overall level of risk. Therefore, combinations involving two low ranks and one medium are consistent with an overall risk estimation ranking of low.

A finding of low risk indicates that the probability of human exposure to resistance is low and the potential human health consequence (if exposure to resistance did occur) is also low. A finding of low risk might also be reached when the potential human health consequence is medium, but only when the potential for human exposure to the resistance is low. Alternatively, the potential for exposure to resistance might be medium, but only when the potential human health consequence is low.

FDA believes that the NADA for certain antimicrobial drugs ranked as medium risk might be considered approvable if FDA can conclude that after evaluating all supporting information there is a reasonable certainty of no harm when the drug is approved under specific use conditions (e.g., such as those outlined for Category 2 drugs). Interpreting the medium risk category of drugs is more complex than the other categories, since the conclusions for the various risk assessment components are potentially more disparate (i.e., ranging from low to high). However, FDA believes it is appropriate to conclude that drugs in this category are associated with a level of risk that is intermediate between the high and low risk category drugs. Therefore, it is consistent to conclude that a finding of reasonably certainty of no harm might be reached for such drugs when use conditions are intermediately restrictive.

As described below, the possible risk management steps range from denying the approval of a drug application (i.e., the drug is unsafe or not shown to be safe) to approving the application under various use conditions that assure the safety of the product.

A. Denying approval of a drug application: The Federal Food, Drug, and Cosmetic Act (FFDCA), Sec. 512(d), and regulations promulgated thereunder (see 21 CFR 514.111), provides possible grounds for denying the approval of a new animal drug application. The statutory grounds for denying approval include the results of tests that show the drug is unsafe or the determination that there is insufficient information as to whether the drug is safe. Consequently, denying the approval of an antimicrobial drug application is one possible outcome of an overall safety evaluation which could include the Qualitative Antimicrobial Resistance Risk Assessment process described above.

B. Drug approval under safe conditions of use: If there are no grounds (as provided for by statute and regulation as described above) for denying the approval of a new animal drug application, FDA will approve the use of the drug under those conditions for which safety and effectiveness has been demonstrated.

   Therefore, use conditions may be approved that are considered consistent with assuring the safety (i.e., with reasonable certainty of no harm) of a given drug in a given category of concern. Drugs considered to be of high concern (with regard to potential human health impact) would typically be associated with more restricted use conditions. Drugs considered to be of lower concern would typically be associated with less restricted use conditions in food-producing animals.

C. The following represent relevant risk management steps or conditions that may be appropriate based on the outcome of the Qualitative Antimicrobial Resistance Risk Assessment process.

   1. Marketing status limitations: Antimicrobial drugs approved for use in animals may be marketed as prescription (Rx), over-the-counter (OTC), or veterinary feed directive (VFD) products. FDA believes that for certain antimicrobial drugs in particular, veterinary supervision is critical to assuring the judicious and safe use of the antimicrobial drug. Therefore, such drugs might be approved for limited use by, or under the supervision of, a veterinarian. For other antimicrobial drugs, the requirement for veterinary supervision may not be warranted.

   2. Extra-label use prohibition: As provided under 21 CFR 530.21(a)(2), FDA may prohibit the extralabel use of an approved new animal drug or class of drugs in food-producing animals if FDA determines that "the extralabel use of the drug or class of drugs presents a risk to the public health." If significant concerns exist regarding assurance of drug safety in light of potential extralabel use, extralabel use may be prohibited according to the procedures described in 21 CFR 530.

3. Extent-of-use limitations: It is recognized that how antimicrobial drugs are used may influence the rate and extent to which resistance emerges. In general, it is believed that increasing the extent to which an antimicrobial drug is used will increase selection pressures for resistance. FDA believes that "extent of use" is an important factor to consider when determining safe conditions of use for an antimicrobial new animal drug. Table 4 integrates method and duration of administration of an antimicrobial drug into a qualitative ranking for "extent of use".

Table 4: Ranking (L, M, H) of extent of antimicrobial drug use in animals based on duration and method of administration

Duration of use	Intended administration to:		
	individual animals	select groups or pens of animals[1]	flocks or herds of animals[2]
Short (<6 days)	**L**[3]	**M**[4]	**H**[5]
Medium (6-21 days)	**L**	**M**	**H**
Long (>21 days)	**M**	**H**	**H**

[1]Administration to select groups/pens of animals involves the delivery of drug to a specific segregated subset of animals within a confinement facility (e.g., administration to a subset of animals within a building, house, feedlot, etc.).

[2]Administration to flocks/herds of animals involves the delivery of drug to all animals within a confinement facility (e.g., administration to all animals within a building, house, feedlot, etc.).

[3]Low, [4]Medium, and [5]High extent of use

D. The following activities are additional important risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals.

1. Post-approval monitoring: Antimicrobial new animal drugs intended for use in food-producing animals are subject to monitoring through the National Antimicrobial Resistance Monitoring System (NARMS).

2. Advisory committee review: When making an approval decision regarding a Category 1 or select Category 2 drugs, FDA may choose to convene an advisory committee to discuss the application.

E. Application of risk management strategies:

The antimicrobial resistance risk assessment described in this guidance document is intended to characterize qualitatively the human health risk associated with the proposed use of a given antimicrobial drug in food-producing animals.

The final step of the risk assessment (i.e., risk estimation) integrates the components of the assessment into a low, medium, or high ranking of the probability of the risk occurring. The risk management strategies discussed in this section of the document are categorized into three levels of concern (i.e., Category 1, 2, or 3). In general, Category 1 includes those drugs ranked "high" in the risk estimation, Category 2 includes those ranked "medium", and Category 3 includes those ranked as "low." However, certain cases may warrant alternative categorization.

Table 5 summarizes potential risk management steps that FDA recommends be considered by the sponsor in proposing use conditions for an antimicrobial drug in a given Category of concern. As illustrated in Table 5, drugs in Category 1 are associated with a high risk ranking and would typically be subject to the most restricted use conditions. Category 3 drugs have a low risk ranking and would typically be subject to the least limitations. Category 2 drugs, ranked intermediate for risk to human health, would typically be subject to limitations that are intermediate between those of Categories 1 and 3.

Note: Category 2 drugs (as described in Table 5) include several approval conditions that may or may not be applied to all drugs in the category. For example, the table indicates that restrictions limiting extra-label use may be considered for certain Category 2 drugs. FDA may consider applying more restrictive risk management steps to those Category 2 (medium risk) drugs that are ranked "high" for consequence assessment *and* ranked "high" for release *or* exposure assessment (see Table 3).

The conditions listed for a given drug category in Table 5 are intended to provide an indication of the conditions of use or limitations that FDA might expect to be associated with a drug product in that category. However, FDA's final determination as to the approvability of specific new animal drug applications will depend on a consideration of all information available for the specific drug application in question. FDA may determine that a proposed drug product can be approved under alternative use conditions/limitations proposed by the sponsor if the sponsor provides adequate information to support the safety of the drug under those conditions.

Table 5. Examples of potential risk management steps associated with the approval of antimicrobial new animal drugs in food-producing animals based on the level of concern (1, 2, or 3) as estimated by a qualitative antimicrobial resistance risk assessment.

	Category of concern		
Approval conditions	**Category 1**	**Category 2**	**Category 3**
Marketing Status[1]	Rx	Rx/VFD	Rx/VFD/OTC
Extra-label use (ELU)	No ELU	Restricted in some cases[3]	ELU permitted
Extent of use[2]	Low	Low, medium	Low, medium, high
Post-approval monitoring	NARMS	NARMS	NARMS
Advisory committee review considered	Yes	In certain cases[3]	No

[1]Prescription (Rx), Veterinary Feed Directive (VFD), Over-the-counter (OTC)

[2]See Table 4 for characterization of extent of use

[3]These risk management steps may be appropriate for certain Category 2 drugs that were ranked high for consequence assessment **and** ranked "high" for release **or** exposure assessment.

Glossary

Antibiotic: Class of substances produced by microorganisms that can kill or inhibit the growth of some groups of microorganisms. In this document the term is meant to refer to chemicals active against bacteria and is used interchangeably with the term antimicrobial.

Antimicrobial: Class of substances that can kill or inhibit the growth of some groups of microorganisms. In this document the term is meant to refer to chemicals active against bacteria and is used interchangeably with the term antibiotic.

Breakpoints: Specific values, expressed relative to terms such as Minimum Inhibitory Concentrations (MICs), or zones of inhibition (which can be correlated with MICs using appropriate statistical methods), which categorize bacteria as clinically susceptible, intermediate or resistant.

Broad-spectrum antibiotic: An antibiotic effective against a large number of bacterial species; generally describes antibiotics effective against both Gram-positive and Gram-negative bacteria.

Commensal bacteria: Bacteria that live continuously on or in certain parts of the body without causing disease under normal circumstances.

Consequence assessment: The consequence assessment describes the relationship between specified exposures to a biological agent (the hazardous agent) and the consequences of those exposures. For the purposes of this risk assessment, FDA has decided that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.

Exposure assessment: The exposure assessment describes the likelihood of human exposure to the released hazardous agent (resistant determinant[s]) through particular exposure pathways. The exposure assessment should estimate qualitatively the probability of this exposure occurring. At this time, assessing human exposure to the hazardous agent will focus on food-related pathways. FDA has decided that human exposure through the ingestion of resistant bacteria from animal-derived foods represents a significant demonstrable pathway for human exposure to resistant bacteria or resistance determinants as consequence of drug use in food-producing animals.

Extra-label: Extra-label use means actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.

Foodborne pathogens: Infectious organisms associated with food-producing animals that can cause disease in humans (e.g., *Salmonella, Campylobacter, E. coli* O157:H7).

Food-producing animals: Animals reared for the production of meat or other food products (e.g., eggs, milk).

Gram-negative bacteria: Bacteria with a cell wall with a structurally distinct outer membrane layer and less peptidoglycan in their cell wall than gram-positive bacteria. Because of the outer layer, they do not retain crystal violet-iodine complex and are thus decolorized by alcohol or acetone enabling them to be counterstained.

Gram-positive bacteria: Bacteria with a predominantly peptidoglycan cell wall. They retain crystal violet-iodine complex when treated with alcohol or acetone and appear deep blue under the microscope.

Hazard: The hazard is defined as human illness that is caused by a specified antimicrobial-resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

Hazardous agent: The hazardous agent is the antimicrobial resistance determinant(s) of human health significance that arises in a food-producing animal as a consequence of animal uses of antimicrobial new animal drugs.

Hazard identification: The process by which one may identify the hazard and the conditions that influence the occurrence of that hazard. This is based upon drug-specific information, bacteria/resistance determinant information, and the methodology for the determination of "resistant" or "susceptible" bacteria.

Microflora: The populations of bacteria normally present in the intestine, body openings, and on the skin.

Minimum inhibitory concentration (MIC): The lowest concentration of an antimicrobial agent, expressed in µg/ml or mg/L that, under defined *in-vitro* conditions prevents the growth of bacteria within a defined period of time.

Minimum inhibitory concentration (MIC) distribution: The range of MICs for a given population of organisms when tested against a specific antimicrobial drug under defined *in-vitro* conditions.

Plasmid: A piece of extrachromosomal DNA much smaller than the bacterial chromosome, usually covalently closed circular molecules. Plasmids exist in the cytoplasm independently of the chromosome and control their own replication.

Release assessment: The release assessment should describe those factors related to the antimicrobial new animal drug and its use in animals that contribute to the emergence of resistant bacteria or resistance determinants (i.e., release of the hazardous agent) in the animal. The release assessment should also estimate qualitatively the probability that release of the hazardous agent would occur. For the purposes of this assessment process, the boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or animal-derived food is collected.

Resistance: A characteristic of a bacterial strain that prevents inhibition by the usually achievable systemic concentrations of an antimicrobial agent with normal dosing schedules and/or falls in the range where specific mechanisms (e.g., beta-lactamases) are likely, and clinical efficacy has not been reliable in treatment studies.

Resistance determinant: A gene that, through either activation, mutation, or external acquisition, provides a bacterium with the necessary biochemical mechanism to survive in the presence of an antimicrobial drug that would otherwise result in the death or inhibition of a susceptible bacterium.

Risk: The probability that human illness is caused by a specified antimicrobial resistant bacteria, is attributable to a specified animal-derived food commodity, and is treated with the human antimicrobial drug of interest.

Risk analysis methodology: The risk analysis methodology described includes hazard identification, risk assessment, risk management, and risk communication.

Risk assessment: The risk assessment process is comprised of a release assessment, exposure assessment, consequence assessment, and risk estimation.

Risk estimate: The risk estimation integrates the components of the risk assessment into an overall conclusion. For the purposes of this document, the risk estimation provides a qualitative indication of the potential risk to human health of a proposed antimicrobial new animal drug. The risk estimation is used for determining appropriate risk management steps.

Risk management: The process of identifying, selecting and implementing measures that can be applied to reduce the level of risk.

Transposon: A small mobile DNA element that carries one or several genes, plus genes encoding for its own transposition between various locations in the bacterial genome.

Veterinary Feed Directive (VFD): A veterinary feed directive is a written statement that authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed containing a VFD drug to treat their animals only in accordance with the FDA-approved directions for use. The VFD category of medicated feeds was created by the Animal Drug Availability Act of 1996 to provide an alternative to prescription status for certain therapeutic animal pharmaceuticals for use in feed.

Zoonotic disease: An infectious disease that is transmissible under normal conditions between animals and humans.

Appendix A

Ranking of antimicrobial drugs according to their importance in human medicine

Objective: This appendix describes a process for ranking antimicrobial drugs with regard to their relative importance in human medicine. This ranking should be considered when completing the *hazard identification* and the *consequence assessment* portions of the qualitative risk assessment outlined in this guidance document. The general criteria for determining the importance ranking are outlined and a preliminary listing of various antimicrobial drugs and assigned rankings is provided.

Ranking process: Based on a consideration of the factors described below, specific antimicrobial drugs or classes of drugs should be ranked as to whether they are of high, medium, or low importance to human medical therapy. The assignment of a high, medium, or low ranking to a given drug or class of drugs is dependent upon the degree to which any one or more of the factors described below is applicable to the drug in question. Table A1 lists antimicrobial drugs and drug classes and suggests a preliminary human importance ranking based on a consideration of the factors described below.

Note: Table A1 does not necessarily include all antimicrobial drugs or drug classes. The development of new drugs for human therapy, the emergence of diseases in humans, or changes in prescribing practices, etc., are among the factors that may cause the importance rankings to change over time. Therefore, it is important that rankings provided in Table A1 be reassessed to confirm that the ranking is consistent with current circumstances. The sponsor may wish to consult with FDA regarding the ranking relevant to their proposed drug at the time the assessment is being completed. New information available may be considered that would alter the ranking listed in this document.

Factors considered in ranking process: In developing criteria for ranking antimicrobial drugs with regard to their importance in human medicine, broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance were considered. Specific factors considered when determining importance include the types of infections treated, the availability of alternative therapies, the uniqueness of the mechanism of action, the ease with which resistance develops and is transferred between organisms, how broadly the agent is used in humans, and the usefulness of the drug in foodborne infections. Note that multiple factors may be applicable to some products, illustrating their considerable importance to human medicine.

Factors related to drug efficacy

1. **Sole or limited available therapy:** Antimicrobial drugs that are the only approved therapy or one of only a few approved therapies available to treat certain very serious human infections are particularly important in human medicine.

Examples include:

- vancomycin and linezolid in the treatment of certain serious infections such as endocarditis, osteomyelitis, or pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA).
- dalfopristin/quinupristin and linezolid in the treatment of serious bloodstream infections caused by vancomycin-resistant enterococcus (VRE) species.

FDA believes that these products should be considered of "high" importance until such time as widespread resistance in humans precludes their use or other suitable alternative agents become available.

2. **Therapy of choice:** There are many more drugs that are not the sole therapy for a disease but are still the preferred choice for therapy for a given infection. Many of these situations are quite important in the management of disease in human medicine.

   These drugs would include those that are central to the treatment of conditions of high morbidity and/or mortality or that are important to public health. An antimicrobial drug may be central to the treatment of a given infection because of efficacy alone, because of a combination of efficacy and tolerability, or because experience with the drug has made it the standard of care for the condition in question. Some drugs have added importance due to their broad use in human medicine. Examples of such drugs are presented below:

   - erythromycin for the treatment of pneumonia caused by *Legionella pneumophila.*
   - ceftriaxone or cefotaxime for the empirical treatment of bacterial meningitis.
   - rifampin for post-exposure prophylaxis of invasive disease caused by *Neisseria meningitidis.*
   - streptomycin for tuberculosis.
   - cefazolin for prophylaxis of post-operative wound infections.

3. **Spectrum of activity of particular importance:** Drugs may also be of importance due to the spectrum of their antimicrobial activity. For instance, the drug may be useful in the treatment of infections due to important, resistant Gram-positive infections. Examples include:

   - vancomycin for methicillin resistant *S. aureus* (MRSA).
   - dalfopristin/quinupristin for vancomycin resistant enterococcus (VRE).
   - beta-lactamase inhibitor combinations for penicillinase or cephalosporinase-producing pathogens.

Drugs useful in the treatment of infections due to important, resistant Gram-negative infections including:

- aminoglycosides and fluoroquinolones for treatment of *Pseudomonas aeruginosa* infections.

4. **Important oral therapy:** The ability to treat serious infections either wholly or in part with oral therapy is quite important in human medicine. This allows for easy outpatient therapy in situations where a patient might otherwise require parenteral and possibly inpatient therapy to complete a full course of treatment. Drug examples include:

   - oral erythromycin or azithromycin for infections due to *Legionella.*
   - fluoroquinolones and trimethoprim-sulfamethoxazole for a variety of infections.

   Drugs in the above situations will often be considered of "high" importance. They may on occasion be considered of "medium" importance depending upon the infections treated and the availability of alternatives.

5. **Important for treating foodborne infections:** Foodborne pathogens offer the most direct link between infection or colonization in animals and infection in humans. Not only are these organisms important for the morbidity they may produce but they offer the opportunity for transmission of resistance elements from animals to humans. The possibility also exists for the transmission of resistance elements within humans and animals from the pathogenic bacteria to other organisms. Therefore, the importance of the drug in treating foodborne infections is an important component of determining its importance for human medicine particularly in the setting of veterinary drug development. These products should typically be considered of "high" importance. This category would include drugs that are the sole or primary treatment for serious foodborne infection. Examples include:

   - quinolones in the treatment of multi-drug resistant *Salmonella* infections
   - expanded-spectrum cephalosporins in the treatment of invasive *Salmonella* infections

   Other drugs may be useful for treatment of foodborne infections, however the disease may not be as severe and/or there are other options for treatment. Such products might be considered either of "high" or "medium" importance. An examples includes:

   - trimethopim-sulfamethoxazole for some *Salmonella* and *Shigella* infections.

6. **Drug with unique mechanism of action:** The mechanism of action of antimicrobials involves the interaction of the drug with specific target molecules within the target organism. The targets of currently approved antimicrobials include inhibition of specific steps in cell membrane function, or cell wall, protein, or nucleic acid synthesis. The development of an antimicrobial with a new and unique mechanism of action unlike that in previously approved drugs is important to the medical community. This is especially true if resistance to the new

antimicrobial is unknown. Limiting the development of such drugs for uses outside of human medicine may be one of the tools to limit the emergence of antimicrobial resistance. Examples include:

- linezolid inhibition of protein synthesis at an earlier step than other currently approved antimicrobial agents

The designation of a unique mechanism is not expected to last indefinitely. For example, when norfloxacin became the first approved fluoroquinolone, its mechanism of action was considered novel. The mechanism of action of new fluoroquinolones may not be considered novel.

However, drugs may have the same target but increased affinity for that target which may still render them unique and valuable in human medicine. For instance, all fluoroquinolones target cellular topoisomerases, including both DNA gyrase and topoisomerase IV. Older quinolones preferentially target DNA gyrase. Newer quinolones have more balanced affinity for both DNA gyrase and topoisomerase IV. This means that unlike the situation with older quinolones, multiple mutations in the genes coding for both topoisomerases might be required before a significant loss of drug activity would occur for newer quinolones.

Initial compounds in a class with a unique mechanism might receive a "high" importance designation. The importance of mechanism on such a designation may be reassessed when multiple products in that class are on the market or when organisms demonstrate significant increases in the rate of antimicrobial resistance in human disease.

Factors related to resistance development

7. **Cross resistance within drug class:** The development of new antimicrobial drugs that are not susceptible to the resistance mechanisms of prior generations of antimicrobial drugs of the same class has been important in preserving options for antimicrobial therapy in humans. Ideally, the development of new drugs within a class of antimicrobials would not encourage the development of antimicrobial resistance to prior generations of antimicrobials in the same class.

   Unfortunately, resistance to newer members of a drug class often predicts resistance to older agents in that class. For example, Gram negative bacteria resistant to streptomycin (an earlier aminoglycoside) would not predict resistance to gentamicin or amikacin (relatively newer aminoglycosides). However, gentamicin or amikacin resistance often predicts resistance to streptomycin. A similar pattern can be seen with cefazolin (a first generation cephalosporin) and ceftriaxone (a third generation agent). Cefazolin resistant organisms are often still susceptible to ceftriaxone, while most ceftriaxone resistant organisms are cefazolin resistant.

"Higher generation" or "extended spectrum" products in such classes might be expected to have a designation of "high" importance. The categorization of initial products in a class would depend upon the particular characteristics of the drug and its use in specific human infections. They could be in any category.

> **Note**: If cross-resistance is known to exist between drugs of differing importance ranking, the drug in question should typically be ranked according to the highest level of importance among the drugs being compared.

8. **Cross resistance across drug classes:** The development of new antimicrobial drugs that are not susceptible to the resistance mechanisms of other classes of antimicrobials are an essential component in preserving our capability to treat resistant infections in humans. Ideally, the development of new antimicrobials in a class of antimicrobials should not encourage the development of antimicrobial resistance to other classes of antimicrobials. Achieving this goal has not been easy.

   Unfortunately, resistance to one class of antimicrobials is often linked to resistance in another class. For example, in Gram negative bacteria resistant to beta-lactam antibiotics, the mechanism of resistance is often inactivation of the drug by a beta-lactamase found on extra-chromosomal elements, e.g., plasmids. Such plasmids may also possess resistance genes to other classes of antibiotics (sulfa drugs, chloramphenicol, etc.). On the other hand, development of resistance to the quinolones occurs via chromosomal mutation of genes encoding efflux or for the cellular topoisomerases that are the target site for this class of drugs. Although a recent report described plasmid-mediated quinolone resistance, chromosomal mutations conferring resistance to quinolones have not been shown to be transferable to other pathogens at the present time[19]. Therefore, antimicrobial drugs that do not confer resistance to other classes of antimicrobial drugs are expected to be considered of greater importance to human medicine.

> **Note**: If cross-resistance is known to exist between drug classes of differing importance ranking, the drug class in question should typically be ranked according to the highest level of importance among the drug classes involved.

9. **Ease of transmissibility of resistance:** The dissemination of resistant determinants via plasmids and transposons is a critical factor in the assessment of the importance of antimicrobials to human medicine. Transmission of resistance may be considered low (relative difficulty of transmission from one organism to another) or high (relative ease of transmission from one organism to another). For the purposes of this guidance, transmissibility of resistance can be defined as follows:

- Low = intrinsic resistance (outer membrane impermeability) or change in target site that is non-transmissible. An example would be fluoroquinolone resistance due to mutation of *gyr A*. or *par C* (topoisomerase IV) or overexpression of chromosomal efflux pumps.
- High = single or multi-drug resistance that is transmissible. One example would be macrolide-lincosamide-streptogramin (MLS) resistance, which confers resistance to macrolides, lincosamides, and streptogramin B classes of antibiotics. This form of resistance has been shown to be transmissible on plasmids and transposons. Plasma mediated ß-lactamases are another example.

Low transmissibility of resistance is clearly more desirable in preserving the usefulness of an antibiotic in human medicine. Products that demonstrate this low transmissibility of resistance are more likely to be ranked of high importance, although a final determination would take into account other characteristics mentioned in this document.

10. **Cross-resistance between drugs used in animals and drugs used in humans:**
In circumstances in which a drug proposed for use in animals is not used in human medicine, but is known to be cross-resistant with a drug that is used in human medicine, the animal drug should typically be assigned the importance ranking of that human drug.

Avoparcin is an example of this scenario. While this drug is not used in human medicine, it belongs to the same class as vancomycin, and resistance to avoparcin could predict resistance to vancomycin. If cross-resistance to avoparcin and vancomycin is demonstrated, one should consider designating avoparcin as a highly important drug as one would vancomycin.

Table A1. Ranking of antimicrobial drugs/drug classes based on the identified relevant factors

Drug class/drug	Human importance rank	Sole Therapy	Drug of Choice	Active for resistant Gram Positives	Active for resistant Gram Negatives	Oral Therapy	Treats Foodborne Infection	Unique Mechanism	No Cross Resistance within Class	No Cross Resistance Across Classes	Low ease of transmissibility of resistance	Serious Infection
Natural penicillins	H											
Benzathine penicillin G												
Penicillin G			x									x
Penicillin V						x						

Drug class/drug	Human importance rank	Sole Therapy	Drug of Choice	Active for resistant Gram Positives	Active for resistant Gram Negatives	Oral Therapy	Treats Foodborne Infection	Unique Mechanism	No Cross Resistance within Class	No Cross Resistance Across Classes	Low ease of transmissibility of resistance	Serious Infection
Penicillinase-Resistant Penicillins	H											
Cloxacillin												
Dicloxacillin						x						
Nafcillin			x									x
Oxacillin			x									x
Antipseudomonal Penicillins	H											
Carbenicillin												x
Mezlocillin												x
Pipercillin												x
Piperacillin/tazobactam				x	x							x
Ticarcillin												x
Ticarcillin/Clavulanate				x	x							x
Aminopenicillins	H											
Amoxicillin				?		x						
Ampicillin			x									x
Ampicillin/Sulbactam					x							x
1st Generation Cephalosporins	M											
Cefazolin												x
Cefadroxil												
Cephalexin						x						
Cephradine												
2nd Generation Cephalosporins	M											
Cefaclor												

Drug class/drug	Human importance rank	Sole Therapy	Drug of Choice	Active for resistant Gram Positives	Active for resistant Gram Negatives	Oral Therapy	Treats Foodborne Infection	Unique Mechanism	No Cross Resistance within Class	No Cross Resistance Across Classes	Low ease of transmissibility of resistance	Serious Infection
Cefaclor-CD												
Cefamandole												
Cefonacid												
Cefprozil												
Cefuroxime						x						x
Lorcacarbef												
3rd Generation Cephalosporins	H								x			
Cefdinir												
Cefixime												
Cefoperazone												
Cefotaxime												x
Cefpodoxime												
Ceftazidime					x							x
Ceftibuten												
Ceftizoxme												
Ceftriaxone			x				x					x
4th Generation Cephalosporins	H											
Cefepime		x			x							x
Cephamycins	M											
Cefotetan												x
Cefoxitin												x
Carbapenems	H											
Imipenem					x					x		x
Meropenem					x					x		x
Monobactams												

Drug class/drug	Human importance rank	Sole Therapy	Drug of Choice	Active for resistant Gram Positives	Active for resistant Gram Negatives	Oral Therapy	Treats Foodborne Infection	Unique Mechanism	No Cross Resistance within Class	No Cross Resistance Across Classes	Low ease of transmissibility of resistance	Serious Infection
Aztreonam	H											
Quinolones	H											
Cinoxacin												
Nalidixic Acid						x	x					
Oxolinic Acid												
Pipemidic Acid												
Fluoroquinolones	H		x	x	x	x	x				x	x
Ciprofloxacin						x	x					
Enoxacin						x						
Gatifloxacin						x						
Grepafloxacin						x						
Levofloxacin						x						
Lomefloxacin						x						
Moxifloxacin						x						
Norfloxacin						x						
Ofloxacin						x						
Sparfloxacin						x						
Aminoglycosides												
Amikacin	H				x+				x			x
Gentamicin	M				x							x
Kanamycin	L											x
Neomycin	L											
Netilmicin	M											
Spectinomycin	M											x
Streptomycin	H		x	x								x
Tobramycin	H	x			x							x

Drug class/drug	Human importance rank	Sole Therapy	Drug of Choice	Active for resistant Gram Positives	Active for resistant Gram Negatives	Oral Therapy	Treats Foodborne Infection	Unique Mechanism	No Cross Resistance within Class	No Cross Resistance Across Classes	Low ease of transmissibility of resistance	Serious Infection
Macrolides	H											
Azithromycin			x			x						
Clarithromycin			x			x						x
Erythromycin						x	x					x
Ketolides	H			x		x						
Telithromycin												
Tetracyclines	M											
Chlortetracycline												
Demeclocycline												
Doxycycline			x			x						x
Minocycline												
Tetracycline												
Glycopeptides	H											
Oritavancin												
Teicoplanin												
Vancomycin		x	x	x								x
Streptogramins	H											
Dalfopristin/ quinupristin		x		x				x				x
Oxazolidones	H											
Linezolid		x		x		x		x				x
Rifamycins	H											
Rifabutin												
Rifampin			x	x		x						x

Other												
Bacitracin	L											
Chloramphenicol	M			x								x
Clindamycin	M			x		x						x
Isoniazid	H		x			x		x				x
Metronidazole	H		x		x	x						x
Polymyxin B	L											
Pyrazinamide	H		x			x						x
Trimethoprim/ sulfamethoxazole	H		x	x		x	x					x

Appendix B

Human exposure to bacteria of human health concern via animal-derived foods

The exposure assessment component of the qualitative antimicrobial resistance risk assessment described in this document includes consideration of consumption patterns in the U.S. population and the prevailing contamination levels in the various animal-derived food commodities. Below are example data sets of these two types of information. The specific information provided is for illustrative purposes. FDA recommends that the sponsor reference data that is most current at the time that the assessment for their product is being conducted.

Per capita meat consumption: Per capita meat consumption data are provided in Table B1. The data presented are for the year 2000 and are published by the USDA Economic Research Service. FDA recommends that the sponsor reference this type of information when completing the risk assessment for their product. The most recent available information should be used for the assessment. The qualitative rankings provided in Table B1 are provisional and represent relative rankings of consumption of the commodities listed for the year 2000.

Food commodity contamination: Prevalence data for *Salmonella* and *Campylobacter* in various animal-derived food commodities are provided in Tables B2 and B3, respectively. FDA recommends that the sponsor reference this type of information when completing the risk assessment for their product. The most recent available information should be used for the assessment. The qualitative rankings provided in Tables B2 and B3 are provisional and represent relative rankings of contamination of the commodities listed.

FDA believes that the concept of qualitatively ranking bacterial contamination in the manner described is consistent with the overall risk assessment process outlined. In addition, FDA believes that the incidence of carcass contamination is a relevant factor for estimating the probability of human exposure to foodborne bacteria. For the purposes of this risk assessment, FDA assumes that a high incidence of carcass contamination is more likely to lead to human exposure through food than a low incidence of carcass contamination. Based on this assumption, FDA believes that it is appropriate to rank qualitatively contamination as low, medium, or high.

The specific criteria for assigning low, medium, or high contamination rankings are provided in footnotes to Tables B2 and B3. These rankings are based primarily on the most recent USDA/FSIS *Salmonella* contamination data cited in Table B2. FDA acknowledges that the calendar year 2001 contamination data listed in Table B2 indicate that all listed food commodities are below their respective *Salmonella* performance standards (i.e., baseline prevalence). For the purposes of the assessment process outlined here, FDA has decided to base the criterion for "high" contamination on the highest level of contamination reported for *Salmonella* in 2001. Therefore, a prevalence of contamination of greater than 25 percent is considered a "high" level of contamination. The medium and low contamination rankings are bracketed at 5 to 25 percent and less than 5 percent, respectively. For consistency, the same ranking criteria may be applied to other bacteria such as *Campylobacter* as described in Table B3.

Ranking human exposure to foodborne pathogen: Table B4 describes a process for integrating the qualitative rankings for food commodity consumption and food commodity contamination into a single human exposure ranking.

Table B1. Per capita consumption data for red meats, poultry, fish and shellfish for the year 2000

Commodity	Per capita consumption* (pounds per capita per year)	Qualitative ranking**
Beef	64.4	High
Veal	0.6	Low
Pork	47.7	High
Lamb and mutton	0.8	Low
Chicken	52.9	High
Turkey	13.6	Medium
Fish and shellfish	15.2	Medium
Total meat	195.2	

*From USDA Economic Research Service[20]; Boneless, trimmed (edible) weight.

**Qualitative ranking based on relative proportion of the total per capita consumption of meat that is attributable to each of the individual meat commodities.

Table B2. Prevalence of *Salmonella* contamination of various animal-derived food commodities and provisional qualitative contamination rankings

Commodity	Baseline prevalence (%)[1]	Calendar Year 2001 Prevalence (%)[1,2]	Qualitative ranking[3]
Broilers	20.0	11.9	Medium
Market hog	8.7	3.8	Low
Cows/bulls	2.7	2.4	Low
Steer/Heifer	1.0	0.6	Low
Ground Beef	7.5	2.8	Low
Ground Chicken	44.6	19.5	Medium
Ground Turkey	49.9	26.2	High

[1]As reported in the USDA/FSIS "Progress Report on *Salmonella* Testing of Raw Meat and Poultry Products, 1998-2001"[21]

[2]Prevalence data for CY 2001 for all size slaughter establishments and establishments that produce raw ground product

[3]Relative qualitative ranking of the level of contamination among various food commodities; Low (< 5%), Medium (5 – 25%), High (> 25%)

Table B3. Prevalence of *Campylobacter* contamination of various animal-derived food commodities and provisional qualitative contamination rankings

Commodity	Prevalence (%)[1]	Qualitative ranking[2]
Broilers	88	High
Turkeys	90	High
Market hog	32	High
Cows/bulls	1	Low
Steer/Heifer	4	Low
Ground Beef	0	Low
Ground Chicken	60	High
Ground Turkey	25	Medium

[1]Data from national surveys conducted between 1992 – 1997.[22-29]

[2]Relative qualitative ranking of the level of contamination among various food commodities; Low (< 5%), Medium (5 – 25%), High (> 25%)

Table B4. Possible process for ranking qualitatively the probability of human exposure to a given bacteria in a given food commodity

	Probability of human exposure to given bacteria		
	per capita consumption of the food commodity		
Probability of food commodity contamination	**High**	**Medium**	**Low**
High	H	H	M
Medium	H	M	L
Low	M	L	L

Appendix C

Re-evaluating the safety of currently approved antimicrobial new animal drugs

I. Objective: FDA intends to re-evaluate the safety of antimicrobial drug products currently approved for use in food-producing animals and for which antimicrobial resistance concerns were not previously considered as described in either Guidance for Industry #78 or the current guidance. This Appendix provides a description of the type of process that FDA intends to use to complete this re-evaluation.

II. Prioritization: To use available resources most effectively, FDA intends to prioritize its efforts to re-evaluate currently approved products. An outline of how this process may be prioritized is described below.

A. Resolve any currently pending regulatory actions (e.g., pending notices of opportunity for a hearing) initiated due to human health concerns associated with antimicrobial resistance.

B. Re-evaluate products currently approved for use in food-producing animals that are ranked "high" with regard to their importance for human medicine and are considered "high" due to their importance for treating foodborne disease in humans (see Appendix A for ranking process).

C. Re-evaluate the other products currently approved for use in food-producing animals that are ranked "high" with regard to importance for human medicine.

D. Re-evaluate products currently approved for use in food-producing animals that are ranked "medium" with regard to importance for human medicine.

E. Consider re-evaluation of products currently approved for use in food-producing animals that are ranked "low" with regard to importance for human medicine.

III. Re-evaluation process: The process of re-evaluating approved antimicrobial new animal drugs may include such elements as the following:

A. The general concepts of the risk analysis methodology described in this document for the pre-approval evaluation of antimicrobial new animal drugs may be applied to the process for re-evaluating currently approved products.

B. FDA may conduct an initial assessment to determine if the safety of the approved product (when used under currently approved use conditions) is brought into question. Based on this assessment, FDA may determine that the drug, under certain use conditions is unsafe or no longer shown to be safe, or that certain use restrictions should be applied in order for that drug to continue to be considered safe. In some cases, FDA may propose to

withdraw the approval of certain drug uses (e.g., certain conditions of use of a product, use in certain animal species, etc.).

C. In the course of conducting the re-evaluation of all currently available information relevant to the NADA(s) in question, FDA may identify additional information that is needed to evaluate safety.

IV. Risk management: FDA intends to apply the same basic risk management strategies outlined for the pre-approval assessment process in the re-evaluation of approved antimicrobial new animal drugs. FDA believes these strategies are appropriate for managing antimicrobial resistance in association with the use of all antimicrobial drugs used in food-producing animals. Based on the assessed risk to human health, FDA actions may:

A. Restrict products currently available over-the-counter (OTC) to prescription or veterinary feed directive use. FDA believes that only those drug products that are of low concern with regard to potential impact on human health may be available OTC.

B. Prohibit extra-label use for certain drug products. In particular, FDA believes that drugs that are of high concern with regard to potential impact on human health may be prohibited from extra-label use.

C. Limit the extent of use of certain antimicrobial drug products, particularly those that are considered to be of high concern with regard to potential impact on human health. For example, whole herd/flock administration or continuous administration of such drug products may not be considered appropriate.

D. Initiate process to withdraw approval of drug product/use condition of concern.

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